REMARKS

Claims 1-3, 6-7, 11-19, 22-23, 26-39, 42-43, 44-52, 54, 56, and 58-63 are pending in the above-identified application and remain for consideration. Claims 58-63 have been added by this amendment. Claims 53, 55, and 57 have been cancelled by this amendment.

Claim 15 was objected to for a minor informality.

Claims 1-3, 6-7, 10-19, 22-23, 26-39, 42, and 45-57 were rejected under the first paragraph of 35 U.S.C. § 112 for lack of compliance with the written description requirement. The Office Action states that, in the view of the Patent Office, that there is no support for the amended concentration ranges in these claims.

Claims 1-3, 6, 10-13, 15-19, 22, 26-29, 31-39, 46-48,50-51, and 52-57 were rejected under 35 U.S.C. § 102(b) as anticipated by PCT Published Patent Application No. WO 95/35390 by Zhang ("Zhang '390") as evidenced by U.S. Patent No. 6,168,922 to Harvey et al. ("Harvey et al. '922"), U.S. Patent No. 5,939,259 to Harvey et al. ("Harvey et al. '259"), or U.S. Patent No. 5,763,185 to Collis et al. ("Collis et al. '185").

Claims 14, 30, and 45 were rejected under 35 U.S.C. § 103(a) as unpatentable over Zhang '390 in view of U.S. Patent No. 5,973,137 to Heath ("Heath '137").

Claims 7, 23, and 42 were rejected under 35 U.S.C. § 103(a) as unpatentable over Zhang '390 in view of U.S. Patent No. 5,030,720 to Bertland et al. ("Bertland et al. '720"). Bertland et al. '720 is cited for the teaching of sodium thiocyanate and sodium perchlorate as chaotropic agents.

Claim 49 was rejected under 35 U.S.C. § 103(a) as unpatentable over Zhang '390, PCT Published Patent Application No. WO 93/03167 by Sigman et al. ("Sigman et al. '167"), Harvey et al. '922, or Harvey et al. '259 each in view of Ahern, The Scientist 9: 1-5 (1995) ("Ahern (1995)").

Claims 1-16 and 52-53 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8 of U.S. Patent No. 6,548,546 to Baker ("Baker '546").

Claims 17-48, 50-51, and 54-57 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8 of Baker '546 in view of Sigman et al. '167.

Claim 49 was rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8 of Baker '546 in view of Ahern (1995).

Claim 49 was also provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 19 of copending Application Serial No. 11/138,543 ("the '543 Application").

Claim 49 was further provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 12-13 and 17-18 of the '543 Application in view of Ahern (1995).

Reexamination of the application as amended, reconsideration of the rejections, and allowance of the claims remaining for consideration are respectfully requested.

The three-month shortened statutory period for response expires on January 13, 2007. Accordingly, this response is being filed in a timely manner.

I. AMENDMENTS TO THE APPLICATION

Entry of the amendments to the application is respectfully requested. As detailed below, these amendments introduce no new matter.

In addition, these amendments comply with the requirements of 37 C.F.R. § 1.116 for amendments made after final rejection. These amendments introduce no new issues, place the claims in better form for allowance, and do not require a new search.

The amendment to claim 15 corrects a minor informality.

The amendments to claims 1, 17, and 37 reduce the maximum concentration of chelator enhancing component (i.e., chaotrope), to less than about 1.25 M. This is a reduction of the previously recited range and is within the range originally disclosed in the specification, e.g., at page 6, line 31 to page 7, line 2.

New claims 58-63 are supported by the specification, for example in Example 1, where suppression of interference is accomplished without the presence of either a substantial concentration of a stabilizer or a substantial concentration of a detergent.

This response is being filed in accordance with recently revised 37 C.F.R. § 1.121, as set forth in 68 F.R. 38611 (June 30, 2003). If the amendment is considered to be not in compliance with recently revised 37 C.F.R. § 1.121, the Examiner is respectfully requested to contact the undersigned at her earliest possible convenience.

Accordingly, entry of the amendments to the claims is respectfully requested.

II. THE OBJECTION TO CLAIM 15

Claim 15 was objected to for a minor informality. Specifically, the phrase "selected from the group" was stated to be duplicated. The duplicate recitation of "selected from the group" has been deleted in this claim by amendment.

III. THE REJECTIONS UNDER THE FIRST PARAGRAPH OF 35 U.S.C. § 112

Claims 1-3, 6-7, 10-19, 22-23, 26-39, 42, and 45-57 were rejected under the first paragraph of 35 U.S.C. § 112 for lack of compliance with the written description requirement. The Office Action states that, in the view of the Patent Office, that there is no support for the amended concentration ranges in these claims. The amended concentration ranges are stated to be new matter.

Specifically, the ranges of chelator enhancing components of "from about 0.1 M to about 1.75M" "from about 0.5 M to about 1.50 M", and "from about 0.5 M to about 1.75 M" are stated to introduce new matter into the claims. Although Applicant has altered the range recited to "from about 0.1 M to less than about 1.25 M" or "from about 0.5 M to less than about 1.25 M," this rejection is still addressed.

This rejection is respectfully traversed. The amended concentration ranges recited in this application are fully supported by the original specification.

In particular, the specification recites, at page 6, line 31 to page 7, line 2: "The amount of the chelator enhancing component is generally in the range of from about 0.1M to 2M, and more desirably the amount of chelator enhancing component in the reagent solution is at least 1M."

With respect to the concentration of chelator, the specification recites, at page 6, lines 19-21: "The amount of the divalent metal chelator is generally present in a reagent solution [in] the range of from about 0.001M to 0.1M. More desirably, the amount of the divalent metal chelator in the reagent solution is at least 0.01M."

The rejection under the first paragraph of 35 U.S.C. § 112 for lack of compliance with the written description requirement, or, alternatively, for new matter, is respectfully traversed.

The general rule, established in In re Wertheim, 191 U.S.P.Q. 90 (C.C.P.A. 1976), is that a narrower range that is completely within a range that is explicitly provided in the specification can be recited in a claim. Such a narrower range is in compliance with the written description requirement of the first paragraph of 35 U.S.C. § 112 and does not constitute new matter. There is no requirement in statute or case law that every intermediate value within the originally-disclosed range needs to be recited explicitly in the specification in order for such an intermediate value to be recited in a claim.

In In re Wertheim, the invention related to a drying method for producing freeze-dried instant coffee. The application disclosed a process in which a coffee extract was prepared by percolating hot water through roasted and ground coffee beans. The extract was concentrated to have a solids content between 25% and 60% and was then charged with gas to produce a foam having a density between 0.4 and 0.8 g/cc. The foam was next frozen and ground into particles, preferably between 0.25 and 2 mm in size. The particles were freeze-dried by standard techniques.

In In re Wertheim, applicant had attempted to claim priority from an earlier-filed foreign application. However, the Examiner refused to allow the priority claim because of alleged lack of compliance with the written description requirement of the first paragraph of 35 U.S.C. § 112. In particular the ranges described in the original foreign application included a range of 25% to 60% for solids content and specific

examples of 36% and 50% for solids content. The subsequently-filed United States application, as to which the Examiner had made the rejection for lack of compliance with the written description requirement of the first paragraph of 35 U.S.C. § 112, claimed ranges of between 35% and 60% and of at least 35%.

On appeal, the Court of Customs and Patent Appeals reversed the rejection with respect to the claimed range of between 35% and 60%, but affirmed the rejection with respect to the claimed range of at least 35%. The Court of Customs and Patent Appeals remarked as follows:

> Broadly articulated rules are particularly inappropriate in this area. . . . Mere comparison of ranges is not enough, nor are mechanical rules a substitute for an analysis of each case on its facts to determine whether an application conveys to those skilled in the art the information that the applicant invented the subject matter of the claims. In other words, we must decide whether the invention appellants seek to protect by their claims is part of the invention that appellants have described as *theirs* in the specification. That what appellants claim as patentable to them is *less* than what they describe as their invention is not conclusive if their specification also reasonably describes that which they do claim.

Id. at 97.

With respect to the claimed range of at least 35%, the Court of Customs and Patent Appeals held that the Patent and Trademark Office had the burden of showing why a person skilled in the art would not recognize in the disclosure a description of the invention defined by the claims. The Patent and Trademark Office was held to have satisfied this burden by pointing out that there was no evidence that concentrations of at least 60% were in fact inherent, and appellants provided no evidence to the contrary. Id. However, this applied only to the circumstance in which the claimed range included

concentrations outside the originally-disclosed range, such as concentrations of 61% or higher.

However, and most importantly, with respect to the narrowed range of between 35% and 60%, the Court of Customs and Patent Appeals held that this range was adequately supported in the earlier-filed foreign application and thus was patentable. As stated by the Court of Customs and Patent Appeals:

> In the context of *this* invention, in light of the description of the invention as employing solids contents within the range of 25-60% along with specific embodiments of 36% and 50%, we are of the opinion that, as a factual matter, persons skilled in the art would consider processes employing a 35-60% solids content range to be part of appellants' invention and would be led by the Swiss disclosure so as to conclude.

Id. at 98.

A similar disclosure was at issue in In re Blaser, 194 U.S.P.Q. 122 (C.C.P.A. 1977), with the same result being reached.

In In re Blaser, the claims at issue involved a chemical process in which an originally-filed application stated a temperature range of from 60° C to 200° C for a particular step in the process. Applicants sought to claim priority from this originally-filed application in a later-filed application. In the later-filed application, the range of this particular step was narrowed to 80° C to 200° C. The Court of Customs and Patent Appeals, following In re Wertheim, held that there was no basis for a rejection of the narrower temperature range under the written description requirement of the first paragraph of 35 U.S.C. § 112 and reversed a rejection on that basis. Id. at 125.

The situation here is completely controlled by the holdings of In re Wertheim and In re Blaser. To put it simply, a range that is completely encompassed by

an originally-filed, broader range is supported by the recitation of the originally-filed range in the specification. The recitation of the narrower range is not new matter and is not properly subject to a rejection under the under the written description requirement of the first paragraph of 35 U.S.C. § 112.

Accordingly, this rejection is respectfully traversed and the Examiner is respectfully requested to withdraw it.

IV. THE REJECTIONS OF CLAIMS 1-6, 8-13, 15-22, 25-29, 31-41, 43-48, 50-51, AND 52-57 UNDER 35 U.S.C. § 102(b) AS ANTICIPATED BY ZHANG '390 AS EVIDENCED BY HARVEY ET AL. '922, HARVEY ET AL. '259, OR COLLIS ET AL.'185

Claims 1-6, 8-13, 15-22, 25-29, 31-41, 43-48, 50-51, and 52-57 were rejected under 35 U.S.C. § 102(b) as anticipated by PCT Published Patent Application No. WO 95/35390 by Zhang ("Zhang '390") as evidenced by U.S. Patent No. 6,168,922 to Harvey et al. ("Harvey et al. '922"), U.S. Patent No. 5,939,259 to Harvey et al. ("Harvey et al. '259"), or U.S. Patent No. 5,763,185 to Collis ("Collis et al. '185").

This rejection is respectfully traversed as applied to the amended claims.

The Office Action stated that the claims were drawn to a method of suppressing the interference of specific agents on a molecular assay of a nucleic acid containing a test sample (independent claims 1 or 17) or a method of improving hybridization of nucleic acids by suppressing specific masking agents (claim 37) comprising contacting the test sample with an amount of a divalent metal chelator and a chelator-enhancing component.

The Office Action further stated that Zhang '390 taught a method comprising adding a lysis buffer containing 2.5 to 5 M guanidine thiocyanate and 100

mM EDTA and 0.5% of a detergent to an equal volume of sample (serum) that contains nucleic acids considered to be test nucleic acids. According to the Office Action, Zhang '390 further taught subsequently adding nucleic acid amplification probes (target nucleic acid) and paramagnetic beads to the solution containing lysis buffer and nucleic acids from the sample. According to the Office Action, Zhang '390 further taught that hybridization occurred between the nucleic acid from the sample and the probes.

The Office Action further stated that Zhang '390 taught that samples for the method included whole blood, separated white blood cells, sputum, tissue biopsies, throat swabbings, urine, or serum.

Zhang '390 was conceded in the Office Action to not specifically teach inhibition of masking agents as set forth in the claim. However, according to the Office Action, Harvey et al. '259 taught that common inhibitors, such as hemoglobin, to nucleic acid amplification could be found in buccal swabs, plasma, serum, sputum, urine, or whole blood samples. Harvey '259 also allegedly taught that chaotropic salts, such as guanidine thiocyanate, could overcome the problem of hemoglobin inhibition. The Office Action further stated that, according to Collis '185, nucleic acid hybridization inhibitory substances were derived from heme or hematin that are commonly found in blood samples. Collis '185 further taught that adding chaotropic agents such as guanidine thiocyanate in samples containing inhibitors overcame this problem.

Zhang '390 is directed to a method for ligation-dependent amplification for the detection of infectious pathogens and abnormal genes. The method involves hybridizing a target nucleic acid to several non-overlapping oligonucleotide probes that hybridize to adjacent regions in the target nucleic acid. The probes are referred to as capture/amplification probes and amplification probes, respectively, in the presence of paramagnetic beads coated with a ligand binding moiety. Through the binding of a ligand attached to one end of the capture/amplification probe and the specific hybridization of portions of the probes to adjacent sequences in the target nucleic acid, a complex comprising: (1) the target nucleic acid; (2) the probes; and (3) the paramagnetic

beads is formed. The probes can be ligated together to form a contiguous ligated amplification sequence bound to the beads, which, upon denaturation to remove the target nucleic acid and unligated probes, can be directly detected or amplified using a suitable amplification technique such as PCR.

The samples are described at page 13, line 31 to page 14, line 2, as follows:

> The present method may be used with routine clinical samples obtained for testing purposes by a clinical diagnostic laboratory. Clinical samples that may be used in the present method include, inter alia, whole blood, separated white blood cells, sputum, urine, tissue biopsies, throat swabbings and the like, i.e.,, any patient sample normally sent to a clinical laboratory for analysis.

The sample is incubated with an equal volume of lysis buffer. The lysis buffer contains a chaotropic agent, a stabilizer, and a detergent, "which provides for the release of any nucleic acids and proteins that are present in the sample" (page 14, lines 19-21). "For example, a suitable lysis buffer for use in the present method comprises 2.5 – 5M guanidine thiocyanate (GnSCN), 10% dextran sulfate, 100mM EDTA, 200mM Tris-HCl (pH 8.0) and 0.5% NP-40 (Nonidet P-40, a nonionic detergent, N-lauroylsarcosine, Sigma Chemical Co., St. Louis, MO)." (page 14, lines 21-26).

The use of an equal volume of sample and lysis buffer means that the final concentrations are 1.25 M to 2.5 M of guanidinium thiocyanate, 5% dextran sulfate, 50 mM of EDTA, 100 mM Tris-HCl, and 0.25% of NP-40. This means that the limitation of the chaotrope to less than 1.25 M avoids anticipation by Zhang '390.

Subsequent to this step, and subsequent to the formation of the complex comprising target nucleic acid-probes-beads, the complex is separated by the use of a magnetic field, and then washed while the magnetic field is still being applied with a

buffer "that contains a chaotropic agent and detergent in amounts that will not dissociate the complex." Such a suitable washing buffer comprises about 1.0-1.5 M GnSCN, 10 mM EDTA, 100 mM Tris-HCl, pH 8.0, and 0.5% NP-40 (page 18, lines 6-8). The buffer wash is stated to "remove unbound proteins, nucleic acids and probes that may interfere with subsequent steps." However, these concentrations should not be able to remove interfering substances, as they are not sufficient to dissociate the complex.

With respect to claims 1-6, 8-9, and 14-16, there is no teaching in Zhang '390 of suppressing interference by a masking agent such as those recited specifically in claim 1. The removal of unbound proteins, nucleic acids, or probes that might interfere with subsequent steps cannot be equated with the removal of a masking agent without a teaching that such a masking agent is in fact removed or its activity suppressed. There is absolutely no teaching or suggestion in Zhang '390 of the removal of a masking agent, as that term is defined in the specification and recited specifically in claim 1. The term "masking agent" in claim 1 and the other independent claims is defined specifically as "selected from the group consisting of leukocyte esterases, myoglobin and hemoglobin analogues, myoglobin and hemoglobin derivatives, myoglobin and hemoglobin oxidation products, myoglobin and hemoglobin breakdown products, ferritins, methemoglobin, sulfhemoglobin, and bilirubin." These masking agents cannot be equated to unbound proteins or probes that might interfere with subsequent steps, as recited in Zhang '390; they are certainly not nucleic acids.

Again, the fact that Zhang '390 taught that wash buffers comprising 1-1.5 M guanidine isothiocyanate and 10 mM EDTA removed unbound proteins that might interfere with subsequent steps does not mean and cannot be equated to the removal of the compounds recited in claim 1 and other independent claims. There is no teaching in Zhang '390 or elsewhere that any of these "unbound proteins" are any of the masking agents recited in claim 1 or other independent claims. Moreover, those wash buffers are not able to dissociate the complex formed in the earlier hybridization/binding step of Zhang '390. If the concentration of chaotropic agent and chelator present in the wash

buffer cannot dissociate the complex, then it will not be able to remove the specific masking agents that are recited, for example, in claim 1.

With respect to claims 37-41 and 43-47, there is again no teaching in Zhang '390 of improvement in hybridization of nucleic acids attributable to the removal or suppression of the specific masking agents recited in these claims. Given that there is no teaching in Zhang '390 of the removal or suppression of the specific masking agents recited in these claims, there can be no basis for asserting that there is improvement in hybridization of nucleic acids attributable to the removal or suppression of these specific masking agents.

Moreover, there is no actual teaching in Zhang '390 that the use of the actual agents recited in the claims of the present application, namely the divalent metal chelator and the chelator enhancing component, is responsible for the removal of any masking agent recited in these claims. To quote Zhang '390 at page 14, lines 21-25:

> For example, a suitable lysis buffer for use in the present method comprises 2.5-5M guanidine thiocyanate (GnSCN), 10% dextran sulfate, 100mM EDTA, 200mM Tris-HCl (pH 8.0) and 0.5% NP-40 (Nonidet P-40, a nonionic detergent, N-lauroylsarcosine, Sigma Chemical Co., St. Louis, MO).

There is no teaching in Zhang '390 that either the guanidine thiocyanate or the EDTA actually removes any masking agent recited in the claims of the present application. To assume this ignores the fact that Zhang '390 also recites the use of dextran sulfate and the nonionic detergent N-lauroylsarcosine. Therefore, there is no proof in Zhang '390 or elsewhere that any effect on any masking agent recited in the claims of the present application is not due to either or both of dextran sulfate or N-lauroylsarcosine.

This point is addressed in new claims 58-63.

In fact, Zhang '390 does actually not teach that either the guanidine thiocyanate or the EDTA actually removes or suppresses the activity of any masking agent recited in these claims. Therefore, there is in fact no showing that the teachings of Zhang '390 "would necessarily improve hybridization because the reagents and methods of Zhang are the same as those encompassed by the instantly claimed invention." The teachings of Zhang '390 do not necessarily lead to this conclusion; if this is an argument for anticipation by inherency, it falls short of the required standard.

The additional references cited, such as Harvey et al. '259, Harvey et al. '922, or Collis '185, do not lead one of ordinary skill in the art to the conclusion that Zhang '390 discloses the method of the present invention. In particular, the fact that Harvey et al. '259 or Harvey et al. '922 teach that common inhibitors for nucleic acid amplification such as hemoglobin can be found in samples such as buccal swabs, plasma, serum, sputum, urine, or whole blood cannot lead to the conclusion that the method claimed in the present invention, with the concentrations of chaotropic agent and chelator recited in the present claims, would necessarily prevent interference from such inhibitors. This is because the mere recitation of the presence of a particular interfering agent, such as hemoglobin, does not necessarily enable one skilled in the art to remove the interfering agent or prevent interference by it if it remains in the reaction mixture.

Harvey et al. '259 or Harvey et al. '922 use absorbent paper that is treated in such a way that nucleic acid samples can be readily eluted from the paper, while interfering substances such as hemoglobin remain on the paper. Harvey et al. '259 or Harvey et al. '922 cannot be read in conjunction with Zhang '390 to reach a conclusion that one can prevent interference by masking agents such as hemoglobin by using, in a solution, the concentrations of chaotropic salt and chelator recited in these claims.

Similarly, Collis et al. '185 relies on removing the masking agent from the cells that are eventually analyzed prior to lysis of the cells. Clearly, in order to amplify the released nucleic acid or perform any other assay involving sequence recognition with

it, one must lyse the cells and then purify the nucleic acid released by lysis of the cells. See claim 1 of Collis et al. '185. Additionally, Collis et al. '185 teaches a variety of agents, such as detergents, and does not state that chaotropic agents are particularly suitable for the prevention of interference by a masking agent such as hemoglobin in a procedure in which the masking agent is not physically separated from the nucleic acid.

Therefore, even if Zhang '390 is interpreted in light of the disclosures of Harvey et al. '259 (or Harvey et al. '922) and Collis et al. '185, there is no basis from which one of ordinary skill in the art can draw a conclusion that the concentrations of chaotropic agent and chelator used in the methods of the present invention can prevent interference by a masking agent such as hemoglobin when the masking agent is not physically separated from the nucleic acid.

Accordingly, the Examiner is respectfully requested to withdraw this rejection as applied to the amended claims.

V. THE REJECTIONS UNDER 35 U.S.C. § 103(a)

A. The Rejection of Claims 14, 30, and 45 Under 35 U.S.C. § 103(a) as Unpatentable Over Zhang '390 in View of Heath '137

Claims 14, 30, and 45 were rejected under 35 U.S.C. § 103(a) as unpatentable over Zhang '390 in view of U.S. Patent No. 5,973,137 to Heath ("Heath '137").

Zhang '390 was stated to teach a method comprising adding a lysis buffer containing 2.5-5 M guanidine thiocyanate and 100 mM EDTA and 0.5% of a detergent to an equal volume of sample (serum) that contains nucleic acids (test nucleic acids) and subsequently adding nucleic acid amplification probes (target nucleic acid) and paramagnetic beads to the solution containing lysis buffer and nucleic acids from the

sample. The Office Action noted that the final concentration of buffer would be 1.25-2.5 M of guanidine thiocyanate and 0.05 M of EDTA after addition of the lysis buffer to the serum sample. The Office Action further noted that Zhang '390 specifically taught that hybridization occurred between the nucleic acid from the sample and the probes. Zhang '390 also taught that the method can be used for detection of genetic variations in samples from patients with genetic diseases or neoplasia. The Office Action further noted that Zhang '390 specifically taught that samples for the method include whole blood, separated white blood cells, sputum, tissue biopsies, throat swabbings, urine, and serum.

Heath '137 was stated to teach that nucleic acid isolation and preservation methods should include anionic detergents, such as SDS or sarkosyl, in a concentration of 0.5% to 3% for the purposes of lysing cells or solubilizing proteins and lipids as well as denaturing proteins. Therefore, according to the Office Action, it would have been *prima facie* obvious to modify the method of Zhang '390 to add SDS or sarkosyl.

Specifically, this rejection is respectfully traversed because the addition of an enzyme inhibitor as taught by Heath '137 does not remedy the deficiencies of Zhang '390.

This is because the addition of the enzyme inhibitor as taught by Heath '137 does not provide for the inactivation of non-enzymatic masking agents, such as hemoglobin. There is no teaching or suggestion that would lead one of ordinary skill in the art to combine the teachings of Heath '137 with those of Zhang '390 when the object of the resulting process would be to prevent interference by masking agents. This is particularly true because nearly all of the masking agents recited in the claims are non-enzymatic. Moreover, even leukocyte esterases, which are enzymes, are not masking agents by virtue of their enzymatic activity.

Additionally, there is no incentive provided by the art to combine the teachings of Heath '137 with those of the other references, because the teachings of

Heath '137 are directed to the isolation of RNA at a low pH, less than 6, and preferably lower. This is a pH that is too low for the performance of an assay such as PCR because it is well below physiological pH and thus is not a suitable pH for the activity of enzymes such as DNA polymerase. The resulting combination, incorporating the teachings of Heath '137, would be inoperable for its intended purpose because the low pH would inhibit the activity of DNA polymerase, which is an essential enzyme in the PCR process. This precludes a finding of obviousness. In re Gordon, 221 U.S.P.Q. 1125, 1127 (Fed. Cir. 1984). A reference must be considered for all that it teaches, including portions that teach away from the claimed invention. Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc., 230 U.S.P.Q. 416, 420 (Fed. Cir. 1986).

Therefore, there is no incentive to combine the teachings of Heath '137 with those of Zhang '390. The absence of such an incentive to combine the references precludes a rejection under 35 U.S.C. § 103. In re Napier, 34 U.S.P.Q. 2d 1782 (Fed. Cir. 1995).

Moreover, Heath '137 does not teach or suggest the use of chaotropic salts at all. Therefore, one cannot arrive at the claimed invention by modifying the teachings of Zhang '390 by anything provided by Heath '137. Thus, even if the teachings of Zhang '390 and Heath '137 are combined, the resulting combination does not yield the claimed invention. In order for an obviousness rejection under 35 U.S.C. § 103 to be proper, the combination of the references must yield the claimed invention, including all significant limitations of the claims. Loctite Corp. v. Ultraseal Ltd., 228 U.S.P.Q. 90 (Fed. Cir. 1985). Because a combination of the teachings of Zhang '390 with those of Heath '137 does not yield the effective chaotropic agent and chelator concentrations recited in these claims, there can be no obviousness rejection under 35 U.S.C. § 103 even if one ignores the fact there is no incentive to combine the teachings of Zhang '390 and Heath '137.

The deficiencies of Zhang '390 were explained in detail above. To summarize, Zhang '390 failed to teach that either the guanidine thiocyanate or the EDTA actually suppresses the effect of any masking agent recited in the claims of the present

application, when those agents are used at the concentrations recited in the claims of the present application. There is no showing that these ingredients actually suppress interference from these masking agents at these concentrations.

Therefore, there is no *prima facie* case of obviousness. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

B. The Rejection of Claims 7, 23, and 42 Under 35 U.S.C. § 103(a) as Unpatentable over Zhang '390 in View of Bertland et al. '720

Claims 7, 23, and 42 were rejected under 35 U.S.C. § 103(a) as unpatentable over Zhang '390 in view of U.S. Patent No. 5,030,720 to Bertland et al. ("Bertland et al. '720"). Bertland et al. '720 was cited for the teaching of sodium thiocyanate and sodium perchlorate as chaotropic agents.

This rejection is respectfully traversed. As applied to the amended claims, no prima facie case of obviousness has been made.

Bertland et al. '720 is recited for the disclosure that sodium thiocyanate and sodium perchlorate are chaotropic agents. However, the combination of the teachings of Bertland et al. '720 with those of Zhang et al. '390 does not yield the claimed invention because there is no basis for the use of the specific concentrations of chaotropic agents recited in these claims. As set forth above with respect to the rejection under 35 U.S.C. § 103(a) with respect to Zhang '390 in view of Heath '137, the absence of a significant limitation of the claimed invention from the teachings of the combination of the references precludes an obviousness rejection. Loctite Corp. v. Ultraseal Ltd., 228 U.S.P.Q. at 90.

Accordingly, the Examiner is respectfully requested to withdraw this rejection.

C. The Rejection of Claim 49 Under 35 U.S.C. § 103(a) as Unpatentable Over Zhang '390, Sigman et al. '167, Harvey et al. '922, or Harvey et al. '259 Each in View of Ahern (1995)

Claim 49 was rejected under 35 U.S.C. § 103(a) as unpatentable over Zhang '390, PCT Published Patent Application No. WO 93/03167 by Sigman et al. ("Sigman et al. '167"), Harvey et al. '922 or Harvey et al. '259 in view of Ahern, The Scientist 9: 1-5 (1995) ("Ahern (1995)").

This rejection is also respectfully traversed as applied to the amended claim. No *prima facie* case of obviousness has been made.

The teachings of Zhang '390 have been described above. As set forth above, Zhang '390 does not teach or suggest that interference from masking agents can be suppressed by the use of chelator enhancing components and chelators at the concentrations recited in this claim. Not only does Zhang '390 fail to teach the specific concentrations recited in this claim as amended, it fails to teach that any suppression of a masking agent is attributable to the chelator enhancing component or chelator, rather than the detergent included in the composition of Zhang '390.

Sigman et al. '167 was stated to teach that there was a need to isolate and prevent degradation of DNA in blood samples from patients suspected of infection with parasites or other infectious agents. Sigman et al. '167 was considered by the Office Action to teach that isolation and storage comprised contacting a biological sample containing DNA in cells with a buffer (aqueous solution) containing a nonamphipathic chaotropic salt (chelator enhancing component) such as guanidine thiocyanate or guanidine chloride and a concentration of a chelating agent such as EDTA. Sigman et al. '167, according to the Office Action, taught that the method was suitable for use on any biological sample including human blood, urine, sputum, and lymphatic fluid. Sigman et al. '167 was considered to teach performing PCR with the preserved nucleic acid.

Harvey et al. '922 and Harvey et al. '259 were considered in the Office Action to teach and claim methods for collecting, storing, and purifying nucleic acids such as DNA or RNA from fluid samples for subsequent genetic characterization by conventional amplification methods. Harvey et al. '922 and Harvey et al. '259 were considered to teach that the device, "903 paper", should be composed of an absorbent material that does not bind nucleic acids irreversibly, impregnated with a chaotropic salt such as guanidine thiocyanate or sodium perchlorate. Harvey et al. '922 and Harvey et al. '259 were considered to specifically teach a method whereby a square of treated paper (treated with guanidine thiocyanate) is added to blood which had been collected in a tube containing EDTA. Harvey et al. '922 and Harvey et al. '259 were considered to teach that DNA was extracted from the paper and subjected to PCR.

Zhang '390, Sigman et al. '167, Harvey et al. '922, or Harvey et al. '259 did not teach the reagents or devices in kit format. However, Ahern (1995) was stated to teach that provided reagents and products in kit format was useful and convenient. The Office Action therefore stated that it would have been *prima facie* obvious to package the reagent of Zhang '390, Sigman et al. '167, Harvey et al. '922, or Harvey et al. '259 in kit form for the purpose of providing convenient premade reagents.

Ahern (1995) is cited for the recitation of a kit format and only for the recitation of a kit format. Ahern (1995) provides no specific information about the selection of reagents or about reagent concentrations for any reaction, including the reactions involved in suppression of interference caused by the masking agents recited in claim 49. Ahern (1995) does not remedy the deficiencies of the primary references, Zhang '390 Sigman et al. '167, Harvey et al. '922, or Harvey et al. '259, which fail to teach suppression of interference by a masking agent in a molecular assay, such as the polymerase chain reaction (PCR) assay at the concentrations of chelator enhancing component and chelator recited in claim 49 as amended.

Accordingly, the combination of Zhang '390, Sigman et al. '167, Harvey et al. '922, or Harvey et al. '259 with Ahern (1995) fails to teach or suggest the claimed

invention in its entirety. For purposes of assessing patentability of a claimed invention over one or more references in terms of nonobviousness, the invention must be viewed as a whole. Jones v. Hardy, 220 U.S.P.Q. 1021 (Fed. Cir. 1984).

The comments at Paragraph 17 of the Office Action fail to support the rejection. The fact that the instructions of the kit carry no patentable weight does not lead to the conclusion that the subject matter incorporated in the kit is in fact obvious. The real issue is that the reagents included in the kit were not shown in the prior art to suppress interference by the masking agents recited in the claim at the concentrations recited in the claim.

Accordingly, the Examiner is respectfully requested to withdraw this rejection.

VI. THE OBVIOUSNESS-TYPE DOUBLE PATENTING REJECTIONS

A. The Rejection of Claims 1-16 and 52-53 Over Claims 1-8 of Baker '546

Claims 1-16 and 52-53 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8 of U.S. Patent No. 6,458,546 to Baker ("Baker '546").

This rejection is respectfully traversed as applied to the amended claims.

The rejection is respectfully traversed, because claims 1-8 of Baker '546 do not recite a method of suppressing interference by a masking agent in a molecular assay. Preservation of a sample cannot necessarily be equated with suppression of interference by a masking agent, particularly with respect to the specific masking agents recited in claim 1. There can be many purposes for preserving a sample, and a sample can be preserved even though masking agents remain in the sample and would interfere

with the performance of an assay such as PCR or hybridization. In fact, without a specific procedure to prevent interference from the masking agents, the masking agents, many of which are proteins as well, such as methemoglobin, would be preserved as well and thus would still be present to create interference with such assays. Therefore, the mere recitation of preservation of the sample does not, in and of itself, imply or suggest suppression of interference by a masking agent such as those recited in claim 1.

Moreover, the specific concentrations of reagents (chelator and chelator-enhancing component) recited in claim 1 are not shown in the claims of Baker '546 to be effective in suppressing interference by a masking agent.

In the absence of any evidence that one of ordinary skill in the art would have equated preservation of a sample with suppression of interference by a masking agent, there can be no basis for an obviousness-type double patenting rejection over claims 1-8 of Baker '546. In re Kaplan, 229 U.S.P.Q. 678 (Fed. Cir. 1986); In re Longi, 225 U.S.P.Q. 651 (Fed. Cir. 1985).

The comments in Paragraph 14 of the Office Action do not support the rejection. It is not accurate to state that the claimed method steps of the instant application encompass the more narrow method steps of Baker '546. There is no teaching of suppression of a masking agent in the claims of Baker '546.

Additionally, there is no specific teaching in the claims of Baker '546 of the narrowed ranges for chelator and chelator-enhancing component (chaotropic salt) recited in these claims. The lack of specific teaching or guidance means that there is no basis for one skilled in the art to select these ranges. This also applies to the other obviousness-type double patenting rejections discussed below. The obviousness-type double patenting rejection is analogous to a rejection under 35 U.S.C. § 103 even though the rejection is not in fact made over that section of the statute. In re Braithwaite, 154 U.S.P.Q. 29 (C.C.P.A. 1967); In re DeBlauwe, 222 U.S.P.Q. 191 (Fed. Cir. 1984). Therefore, the lack of specific teaching or guidance enabling one skilled in the art to

select these ranges mandates a finding of no obviousness-type double patenting. Cf. In re Baird, 29 U.S.P.Q. 2d 1550 (Fed. Cir. 1994); In re Jones, 21 U.S.P.Q. 2d 1941 (Fed. Cir. 1992) (no obviousness under 35 U.S.C. § 103 when prior art does not provide guidance to particular species within relatively large genus disclosed by prior art).

Accordingly, the Examiner is respectfully requested to withdraw this rejection.

B. The Rejection of Claims 17-48, 50-51, and 54-57 Over Claims 1-8 of Baker '546 in View of Sigman et al. '167

Claims 17-48, 50-51 and 54-57 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8 of Baker '546 in view of Sigman et al. '167.

This rejection is also respectfully traversed as applied to the amended claims.

To the extent that the amendments to claim 17 have not obviated this rejection, it is respectfully traversed, essentially for the reasons stated above with regard to the obviousness-type double patenting rejections of claims 1-8 over Baker '546. The obviousness-type double-patenting rejection is considered to be analogous to a prior art rejection under 35 U.S.C. § 103, and there is no teaching of the methods of claim 17-36, even if Baker '546 and Sigman et al. '167 are combined. As demonstrated above, Sigman et al. '167 does not disclose or suggest the suppression of interference by a masking agent or the improvement of a signal response in a molecular assay due to the suppression of interference by a masking agent specifically recited in these claims. Sigman et al. '167 does not teach the suppression of interference by the specific masking agents recited in claim 1. In fact, it is completely silent with respect to these masking agents.

As stated above, the claims of Baker '546 do not teach or suggest the suppression of interference by the specific masking agents recited in these claims. Therefore, the combination of Baker '546 and Sigman et al. '167 does not result in the claimed invention, and there is no basis for this obviousness-type double patenting rejection. Additionally, the claims of Baker '546 do not teach or suggest the specific ranges recited in these claims.

Accordingly, the Examiner is respectfully requested to withdraw this rejection.

C. The Rejection of Claim 49 Over Claims 1-8 of Baker '546 in View of Ahern (1995)

Claim 49 was rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8 of Baker '546 in view of Ahern (1995).

This rejection is also respectfully traversed as applied to claim 49 as amended.

Ahern (1995) is merely cited for the teaching that kits are convenient and can be readily used to perform many procedures. Given that Baker '546 does not and cannot teach the suppression of the specific masking agents recited in claim 49 as amended or the concentrations of chelator and chelator enhancing component recited in claim 49 as amended, the mere teaching that a kit can be prepared does not remedy the deficiency of the teachings of Baker '546, as explained above.

The obviousness-type double-patenting rejection is again considered to be analogous to a prior art rejection under 35 U.S.C. § 103, and there is no teaching of the kit of claim 49, even if claims 1-8 of Baker '546 and Ahern (1995) are combined.

Accordingly, Applicant respectfully requests that this obviousness-type double patenting rejection be withdrawn.

D. The Provisional Rejection of Claim 49 Over Claim 19 of the '543 Application

Claim 49 was also provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 19 of copending Application Serial No. 11/138,543 ("the '543 Application").

To the extent that the amendments to claim 49 have not obviated this rejection, it is respectfully traversed.

This rejection is respectfully traversed because there is no teaching or suggestion of the suppression of the specific masking agents, or of the concentrations of the chelator and chelator enhancing component, recited in claim 49 of the present application in claim 19 of the '543 Application. As stated above, such obviousness-type double-patenting rejections are again considered to be analogous to a prior art rejection under 35 U.S.C. § 103. The lack of teaching of the specific masking agents recited in this claim means that there is no obviousness-type double patenting.

E. The Provisional Rejection of Claim 49 as Unpatentable over Claims 12-13 and 17-18 of the '543 Application in View of Ahern (1995)

Claim 49 was also provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 12-13 and 17-18 of the '543 Application in view of Ahern (1995).

To the extent that the amendments of claim 49 have not obviated this rejection, it is respectfully traversed.

This rejection is respectfully traversed because there is no teaching or suggestion of the suppression of the specific masking agents, or of the concentrations of the chelator and chelator enhancing component, recited in claim 49 in claims 12-13 or 17-18 of the '543 Application. As indicated before, Ahern (1995) is cited merely for the possibility of kits, but does not provide the necessary information to result in an obviousness-type double patenting situation for this claim. Again, such obviousness-type double-patenting rejections are again considered to be analogous to a prior art rejection under 35 U.S.C. § 103. The lack of teaching of the specific masking agents recited in this claim means that there is no obviousness-type double patenting.

Accordingly, the Examiner is respectfully requested to withdraw this rejection.

VII. CONCLUSION

In conclusion, all claims remaining for consideration are novel and non-obvious over the references of record, whether considered individually or in combination. The claims are supported by the specification and do not introduce new matter. These claims are not subject to obviousness-type double patenting. Accordingly, prompt allowance of these claims is requested.

If any issues remain, the Examiner is respectfully requested to telephone the undersigned at (858) 450-0099 x302.

Respectfully submitted,

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